United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: Propoxycarbazone-sodium
Reason for Issuance: Conditional Registration
Date Issued: June 30, 2004

DESCRIPTION OF CHEMICAL

Generic Name:	methyl 2-[[[(4,5-dihydro-4-methyl-5-oxo-3-propoxy-1H-1,2,4-triazol-1-yl)carbonyl]amino]sulfonyl]benzoate, sodium salt
Common Name:	Propoxycarbazone-sodium
Trade Names:	Olympus™ 70% Water Dispersible Granule Herbicide
EPA Chemical Code:	122019
Chemical Abstracts Service (CAS) Number:	181274-15-7
Year of Initial Registration:	2004
Pesticide Type:	Herbicide
U.S. and Foreign Producers:	Bayer CropScience P.O. Box 12014 2 T.W. Alexander Drive Research Triangle Park, NC 27709

USE PATTERNS AND FORMULATIONS

Propoxycarbazone-sodium will be applied post-emergence through ground or aerial application equipment to wheat. Propoxycarbazone-sodium has herbicidal activity against certain grasses and broadleaf weeds. It's efficacy is the result of the inhibition of the enzyme acetolactate synthase (ALS) enzyme in target plants.

SCIENCE FINDINGS

SUMMARY

Hazard and risk assessments were conducted in relation to this registration application and tolerance petition for propoxycarbazone-sodium on wheat that suggest that its use, consistent with the proposed labeling measures, will be protective of the public health and the environment. There are no other registrations for this chemical. Therefore, aggregate exposures to the general public are based on food plus water calculations derived from this use.

In estimating risks from this use, the Health Effects Division (HED) in EPA used conservative Tier 1 exposure assumptions. Tolerance level residues and 100 percent crop treated exposure assumptions were used in this risk analysis. An acute risk assessment was not calculated because no suitable endpoint was selected which could be attributable to a single-dose exposure.

Propoxycarbazone-sodium has low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category IV). It is not an eye or dermal irritant or a dermal sensitizer. No toxicity was seen at the limit dose in a 28-day dermal toxicity study in rats. The main target organ appears to be GI tract (gastric irritation) in the 2-generation reproduction toxicity study in rats, developmental toxicity study in rabbits, and the 90-day feeding study in rats. In the 64- day and 1-year toxicity studies in dogs, no toxicity was observed at doses ≥1181 mg/kg/day and ≥605 mg/kg/day, respectively. Increased incidence of gastric irritation was observed at a very high-dose (limit dose) in a 90-day feeding study in rats. While in a combined chronic toxicity/carcinogenicity study in rats, decreased body weight, increased urinary pH and histopathological changes in the kidney (foci of mineralization of pelvis, dilated and cystic renal tubules filled with proteinaceous material, regenerative tubular epithelium, glomerular and interstitial fibrosis, and hyperplasia of the pelvic epithelium). These effects are indicative of the kidney as the target organ. Effect on body weight was evident in both subchronic and chronic toxicity studies in mice.

There is no evidence of neurotoxicity in any study. No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rats or rabbits in developmental studies. No quantitative or qualitative evidence of increased susceptibility was seen following pre/post natal exposure to rats in 2-generation reproduction toxicity study in rats. No evidence of carcinogenicity was observed in a carcinogenicity study in mice at doses up to the limit dose. In a chronic toxicity/carcinogenicity study in rats, there was an increase in the incidence of mononuclear cell leukemia (MNCL) in mid- and high-dose males. HED concluded that MNCL in male Fischer 344 rats was <u>not</u> treatment-related. In accordance with the EPA Proposed Guidelines for Carcinogen Risk Assessment (JUL-1999), HED classified propoxycarbazone-sodium as based on lack of carcinogenicity in mice and rats and negative findings in various mutagenicity assays. Quantification of human cancer risk is not required, propoxycarbazone-sodium and its selected metabolites were negative for mutagenicity in various mutagenic assays.

Propoxycarbazone-sodium was rapidly absorbed from the GI tract of rats following oral dosing. There were no major sex-related differences in the pattern of excretion. Approximately

23-26% and 31% of the administered oral dose was absorbed in male and female rats, respectively. The radiolabeled test material was primarily eliminated unchanged in the urine and feces (~75-88% of the administered dose), with essentially none eliminated by the lungs. Of the absorbed radiolabeled test material, ~90% was excreted into the urine while the remaining was recovered from the bile.

Risks to agricultural workers were also considered. HED determined that short- and intermediate-term exposures may occur. Since propoxycarbazone-sodium may be applied only twice per year, long-term exposures are not expected from the proposed uses. No more than 30 days exposure are expected for most handlers. It might be possible for commercial applicators to experience intermediate-term exposures (1-6 months). The worst case occupational risk for intermediate-term operations with aerial application is 150,000 Margin of Exposure (MOE). A MOE ≥100 is sufficient to protect occupational pesticide handlers. Since the estimated MOEs are all >100, the proposed use does not exceed HED's level of concern (LOC).

The Environmental Fate and Effects Division (EFED) in EPA has reviewed this action and concluded Based on EFED's screening-level Tier 1 ecological risk assessment, only Terrestrial Plants are directly at risk from the proposed use of propoxycarbazone-sodium on wheat. All other organisms, including aquatic and terrestrial animals, beneficial insects, and aquatic plants, are presumed not to be at *direct* risk. This is logical, based on the fact that the mode of action (inhibition of the acetolactate synthase or ALS enzyme), is specific to plants. Aquatic plants are not at risk because the modeled exposures in water are far below the measured effect levels. . Bayer CropScience is a member of the Endangered Species and Spray Drift Task Forces and any measures developed by the Task Forces to mitigate risks to non-target plants will be applied to propoxycarbazone-sodium as well as other registered herbicides.

SCIENTIFIC FINDINGS

EPA reviewed the submitted product chemistry, toxicology, residue chemistry, occupational exposure, ecological effects and environmental fate data. A summary of these assessments follows:

Health Effects Division's Review- Hazard Identification

Propoxycarbazone-sodium has low acute toxicity via the oral, dermal, and inhalation routes. It is a not a eye irritant, a dermal irritant or a dermal sensitizer. No toxicity was seen at the limit dose in a 28-day dermal toxicity study in rats. The main target organ appears to be GI tract (gastric irritation) in the 2-generation reproduction toxicity study in rats, developmental toxicity study in rabbits, and the 90-day feeding study in rats. In the 64- day and 1-year toxicity studies in dogs, no toxicity was observed at doses ≥1181 mg/kg/day and ≥605 mg/kg/day, respectively. Increased incidence of gastric irritation was observed at a very high-dose (limit dose) in a 90-day feeding study in rats. While in a combined chronic toxicity/carcinogenicity study in rats, decreased body weight, increased urinary pH and histopathological changes in the kidney (foci of mineralization of pelvis, dilated and cystic renal tubules filled with proteinaceous material, regenerative tubular epithelium, glomerular and interstitial fibrosis, and hyperplasia of the pelvic epithelium). These effects are indicative of the kidney as the target organ. Effect on body weight was evident in both subchronic and chronic toxicity studies in mice.

An endpoint of concern attributable to a single dose (exposure) was not identified from the available studies. An acute RfD was not established. Therefore, there is no acute reference dose (aRfD) or acute population adjusted dose (aPAD). The short-term incidental oral and inhalation endpoint is based upon GI toxicity (enlarged cecum, reduced and light-colored feces). There is no short-term dermal endpoint since there are no developmental concerns and no evidence of system toxicity in 28-dermal study. The intermediate-term endpoints for oral and inhalation routes of exposure are based upon microscopic lesions of the stomach in parental male rats observed in the reproduction study. There is no intermediate-term dermal endpoint since there are no developmental concerns and no evidence of system toxicity in 28-dermal study. The chronic RfD is 0.748 mg/kg/day and the chronic population adjusted dose (cPAD) is 0.748 mg/kg/day. Propoxycarbazone-sodium is classified as "not likely to be carcinogenic to humans" based upon lack of evidence of carcinogenicity in rats and mice. Therefore, a cancer risk assessment is not required.

FQPA Decision

The toxicology database is complete for FQPA purposes and there are no residual uncertainties for pre-/post-natal toxicity. Based on the quality of the exposure data, EPA determined that the 10X SF to protect infants and children should be removed. The FQPA factor is removed based on the following:

- There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to in utero exposure to propoxycarbazone-sodium in developmental toxicity studies. There is no quantitative or qualitative evidence of increased susceptibility to propoxycarbazone-sodium following pre-/post-natal exposure to a 2-generation reproduction study.
- There is no concern for developmental neurotoxicity resulting from exposure to propoxycarbazone-sodium. A developmental neurotoxicity study (DNT) study is not required.
- The toxicological database is complete for FQPA assessment.
- The chronic dietary food exposure assessment utilizes HED-recommended tolerance level residues and 100% CT information for all commodities. By using these screening-level assessments, actual exposures/risks will not be underestimated.
- The dietary drinking water assessment utilizes water concentration values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded.

A chronic dietary exposure analysis was conducted using Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™), which incorporates food consumption data as reported by respondents in the USDA 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and accumulated exposure to the chemical for each commodity. The following assumptions were made for the chronic exposure assessments: For the chronic analyses, tolerance-level residues were assumed for all food commodities with current or proposed propoxycarbazone-sodium tolerances, and it was assumed that all of the crops included in the analysis were treated. Percent Crop Treated (PCT) and/or anticipated residues were not used in the chronic risk assessment. The chronic dietary food exposure estimates were less than HED's level of concern (<100% cPAD) for the general U.S.

population and all population subgroups. Specifically, the most highly exposed population subgroup was "Children 1-2 years old" at < 1% of the cPAD.

Drinking Water

The Agency lacks sufficient monitoring exposure data to complete a comprehensive dietary exposure analysis and risk assessment for propoxycarbazone-sodium in drinking water. Because the Agency does not have comprehensive monitoring data, drinking water concentration estimates are made by reliance on simulation or modeling taking into account data on the physical characteristics of propoxycarbazone-sodium.. The estimated environmental concentrations (EECs) for surface water [from FQPA Index Reservoir Screening Tool (FIRST)] are 2.3 ppb and 0.9 ppb for the acute and chronic scenarios, respectively. The EEC for ground water [from SCI-GROW (Screening Concentration in Ground Water) modeling] is 0.4 ppb to be used for both acute and chronic scenarios. All the EEC values are less than the lowest drinking water levels of concern (DWLOC) value of 7,480 ppb (specifically for the "children 1-6 years old" sub-population) determined for the chronic scenario, and therefore do not exceed HED's level of concern.

Consideration of Risks to Pesticide Applicators and Handlers

The proposed use of the herbicide Olympus™ 70% Water Dispersible Granule Herbicide, a suspension concentrate formulation containing 40% of the active ingredient (a.i.), propoxycarbazone-sodium, is for pre- and postemergence control of broadleaf weeds in wheat. Propoxycarbazone-sodium may be applied either by ground sprayers or by aerial application up to corn height of 30" tall. A maximum of two applications per season and 0.43 lbs a.i./A/season are proposed. For preemergence application, Olympus™ 70% Water Dispersible Granule Herbicide is proposed for use at 0.188-0.24 lbs ai/A by groundboom. In a single postemergence application, 0.094 lbs a.i./A should not be exceeded.

Based on the proposed use patterns, short-term dermal and inhalation exposures are expected for private applicators (farmers treating their own crops) and commercial applicators. Since no chemical-specific data are available to assess potential exposure to workers, the exposure and risk assessment presented in this document are based on the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998). The maximum application rate listed on the label was used for all calculations. The standard values for acreage were taken from HED Exposure Science Advisory Committee (Expo SAC) Policy #09, effective 5-JUL-2000. Both the low and high number of acres treated per day were used to demonstrate a range of potential exposure. When wearing the label required personal protective equipment (PPE) (single layer of clothing and gloves), all Margins of Exposure (MOEs) do not exceed HED's level of concern, with the exception of the intermediate-term mixer/loader in support of aerial application.

Currently it is HED's draft policy that short-term endpoint durations may be increased to 30 days on a case by case basis. In the case of propoxycarbazone-sodium, the same endpoint [rat developmental endpoint (LOAEL = 100 mg/kg/day)] is still appropriate for the 0 to 30 day exposure period since it provides protection for developmental effects seen below maternally toxic doses. For the proposed use of propoxycarbazone-sodium, no longer than 30 days of

exposure is expected for both private and commercial handlers. Using the redefined exposure durations, all MOEs for handler of propoxycarbazone-sodium are below HED's level of concern.

There is a potential for agricultural workers to experience post-application exposure to pesticides during the course of typical agricultural activities. However, the HED did not identify short- or intermediate-term dermal toxicological endpoints. There is a 12-hour REI for propoxycarbazone-sodium. HED believes post-application inhalation exposure to propoxycarbazone-sodium would be negligible; therefore, the proposed use does not exceed HED's LOC.

Environmental Fate and Effects Division's Review

Propoxycarbazone-sodium is expected to degrade in soil by metabolism and abiotic processes. Hydrolysis is slow. Laboratory experiments of aqueous photolysis in pH 7 water indicate environmental half-lives of 37 to 94 days at 40°N latitude. Soil photolysis experiments gave environmental half-lives of 38 to 70 days at 40°N latitude.

Soil metabolism experiments gave half-lives of 77 to 103 days. Experiments with German soils gave half-lives of 9 to 21 days, 16 to 47 days and 80 to 224 days. Aqueous metabolism experiments indicate that the degradate propoxycarbazone-carboxylic acid is formed in large amounts (>50% of applied radiation) and is stable through the end of the experiment (100 or 365 days).

Its high water solubility (42,000 ppm) and low volatility (vapor pressure $<1 \times 10^{-8}$ Pa at 20° C) indicate very little tendency to evaporate from water or moist soil. The high water solubility and low soil partitioning coefficients (Kd = 0.22 to 1.71) indicate that it is very mobile in soil, so leaching and run-off are potentially important routes of dissipation. However, field dissipation and lysimeter studies show that the parent compound does not leach below about one foot in depth before being degraded.

The sorption behavior of propoxycarbazone and six of its degradates is more closely correlated to the clay content of soil than to the organic carbon content, as is usually the case for neutral, non-polar organic compounds. This is consistent with the fact that propoxycarbazone is anionic (negatively charged) after the dissociation of the sodium salt. The desorption coefficients are generally higher than the adsorption coefficients, meaning that there is more resistance to the desorption process.

The "intact" degradate of propoxycarbazone is propoxycarbazone-carboxylic acid, which results from the loss of a methyl ester group, but has the intact sulfonylurea bridge. This degradate was quite stable in aerobic and anaerobic aqueous metabolism studies, with 50% or more of the applied radiation at the end of 100-day or 365-day experiments. There may be some concern for the persistence and accumulation of this degradate in ponds, lakes, and reservoirs.

There are two sets of degradates that result from the cleaving of the sulfonylurea bridge. These include the triazolinones, and the sulfonamide/saccharins. The former include N-methylpropoxytriazolinone amide and N-methylpropoxytriazolinone, which was a major degradate in all soil metabolism studies. The latter include propoxycarbazone-sulfonamide

methyl ester, sulfonamide acid, saccharin itself and 4-hydroxysaccharin. All of these were major metabolites in soil or aquatic metabolism experiments. With the exception of 4-hydroxysaccharin, all are of equal or greater mobility than the parent.

Terrestrial field dissipation studies were conducted in the USA and in Europe. Leaching of parent propoxycarbazone was not observed below the 6- to 12-inch layer. Volatilization was not measured, but was not expected based on the low vapor pressure. Field dissipation half-lives were in the range of 4 to 54 days.

Propoxycarbazone-sodium has been determined to be practically non-toxic to birds and small mammals, to honey bees, to warm and cold water fish, and to daphnids. EFED's judgement is that propoxycarbazone-sodium is unlikely to present a risk to aquatic and terrestrial animals on an acute or chronic basis for the tested species. Loss of habitat and food items may indirectly affect terrestrial and aquatic organisms as a result of damage to non-target plants from off-target transport. There is a concern for non-target terrestrial and aquatic plants from the proposed use. Non-target plants may be exposed to propoxycarbazone-sodium by spray drift and runoff. Labeling statements will advise users about the risks to non-target plants. County Restrictions and Buffer Zones are required to protect endangered plant species and non-target plants. Bayer CropScience is a member of the Endangered Species and Spray Drift Task Forces which are addressing the issue of toxicity to non-target organisms. Registration will be limited to two years.

OUTSTANDING DATA

The following details the data gaps and/or additional information required from the registrant:

Chemistry

- Additional storage stability data for mustard greens and turnips to validate the submitted field rotational crop study.

Environmental Fate and Effects

- Monitoring of "carboxylic acid" degradate to determine if it is accumulating in ponds, lakes and reservoirs near propoxycarbazone use areas.

PUBLIC INTEREST FINDING:

Olympus™ 70% Water Dispersible Granule Herbicide is an effective in controlling winter annual brome species, jointed goatgrass, wild oat and several broadleaf weeds in wheat. It will fill a niche in situations where crop rotation is not feasible or growers need more management flexibility. Also, there are currently few options available for control of jointed goatgrass, a difficult weed for winter wheat growers. It suppresses jointed goatgrass if sequential applications are made. There is no evidence of carcinogenicity in the mice or rat studies conducted with propoxycarbazone-sodium.

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

Registering propoxycarbazone-sodium will meet the objectives of GPRA title 3.1.1 by assuring new pesticides that enter the market are safe for humans and the environment and title 4.1.2 by reducing environmental exposure to herbicides.

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